REMARKS

Claim 1 is pending in this application. Claim 1 has been rejected. Claim 1 has been amended. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claim 1 has been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner suggests that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner suggests that the specification lacks support for the administration of methotrexate "every other day for up to 11 days", pointing to pages 5 and 6 of the specification as filed. The Examiner suggests that at those pages it is taught that the first two doses are every day. Applicant respectfully disagrees with the Examiner's conclusions regarding the teaching of the specification.

Contrary to the Examiner's suggestion, at page 5 of the specification as filed it is taught that rats received doses of methotrexate no sooner than every other day. At page 5, lines 27-33, the dosing of methotrexate in animals with radiculopathy is taught (Group A and Group B rats). There it is stated that methotrexate was administered intrathecally to the surgical area "immediately following surgery, followed by additional methotrexate administration locally at days 2 and 4 post-surgery" (the same regimen was used for both Group A and B rats). In this case, the surgery day would be day 0, not day 1. Day 1 would mean one day after surgery. So, these rats were indeed administered methotrexate every other day, *i.e.*, days 0, 2 and 4. However, in an earnest effort to advance the prosecution and facilitate allowance of the claim, Applicant has amended claim 1 to recite that methotrexate is administered "every other day for up to 4 days", which is exactly the same as the protocol shown here at page 5 of the specification as filed. Accordingly, the claim as amended meets the requirements of 35 U.S.C. 112, first paragraph and withdrawal of this rejection is respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 103(a)

Claim 1 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Yaksh et al. (U.S. Patent No. 6,180,716; hereafter referred to as the '716 patent) and Heywood et al. (1988), and further in view of *Drug Facts and Comparisons* (1994). The Examiner has suggested that the '716 patent teaches that spinal (intrathecal/epidural) administration of centrally acting agents, such as anti-neoplastics and analgesics, have considerable therapeutic efficacy for treatment of pain, spasticity, central nervous system tumors, and infections, and further that methotrexate is one of these centrally acting agents that is given by intrathecal infusion. The Examiner further suggests that Heywood et al. (1998) teach that rheumatoid arthritis causes cervical spine instability and is a causative factor in symptoms of radiculopathy while *Drug Facts and Comparisons* (1994) teach administration of methotrexate for rheumatoid arthritis by ameliorating symptoms of inflammation (pain, swelling stiffness) at doses of from 7.5 mg/week to 15 mg/week. As a result, the Examiner suggests it would have *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to administer methotrexate intrathecally at the doses claimed (1 mg/kg every other day for up to 11 days)

for treatment of lower back pain with radiculopathy because motivation is provided by the teaching of the '716 patent (teaching methotrexate intrathecally) and Heywood et al. (1988; teaching rheumatoid arthritis causes cervical spine instability and is a causative factor in symptoms of radiculopathy) combined with the teaching of *Drug Facts and Comparisons* (1994; teaching that methotrexate is routinely used to treat rheumatoid arthritis to ameliorate symptoms of inflammation at doses of from 7 to 15 mg/week). Further, the Examiner suggests that in terms of the dose cited in the claim, *Drug Facts and Comparisons* teaches that administration of methotrexate at a dose of 7.5 mg/week could readily be extrapolated by one of skill to an intrathecal dosage to fit the limitation of an animal. The Examiner then states that an animal weighing 7.5 kg is treated (1 mg/kg x 7.5 mg = 7.5 mg), pointing to the fact that the claim states "an animal" which could be that large.

Applicants respectfully disagree with the Examiner's conclusions regarding the combination of cited references, especially as it concerns the issue of dose. In the specification as filed, the Examiner points out that the animal mentioned and discussed is a rat. As already discussed in previous Office Action Replies, a rat does not weigh 7.5 kg. In fact, a rat

typically weighs much less than 1 kg (200-300 g is typical for young adult rats), which is a well-known fact for one of skill in the art. Thus, 200 g x 1 mg/kg (0.2 kg x 1 mg/kg = 0.2 mg) is a dose much less than the 7.5 mg that is taught in *Drug Facts and Comparisons*, i.e., only 0.2 mg. Therefore, contrary to the Examiner's suggestions, the dose information provided in that reference is NOT sufficient for one of skill to choose a dose for testing in animals. Giving 7.5 mg to a rat would be equivalent to 7.5 mg x 1/0.2 kg or 37.5 mg/kg, a dose that would likely be lethal in a rat since the injected LD_{50} of methotrexate for a rat is known to be in the range of 6 to 25 mg/kg (see http://www.medsafe.govt.nz/profs/datasheet/m/Methotrexateinjmayne.htm). Thus, contrary to the assertions by the Examiner, one of skill would not be able to use the references cited to identify a dose to use as claimed in the instant invention.

This is further an issue if one of skill were to use the human dose teaching cited by the Examiner as a guide to use in the method of the present invention and actually try to treat humans. Using the prior art teaching cited by the Examiner, one of skill would assume that 7.5 to 15 mg/week of methotrexate would be a satisfactory dose for treatment of pain if used intrathecally. However, the claim as amended stipulates that the

dose to be used in an animal that would include a human, by definition, would be 1 mg/kg or 70 mg per day and 210 mg per week. Clearly, one of skill would not understand to use this dose that is supported by the teachings of the specification as filed and instead would be using a dose that is much less. As already discussed *supra*, Applicant has amended the claim to recite that the dose of methotrexate of 1 mg/kg is administered every other day for up to 4 days. Support for this amendment to the claims can be found at page 5 of the specification as filed where it is taught that the drug was administered to rats every other day for up to 4 days. Applicant also respectfully points out, as already discussed supra, that the dosing in rats taught on page 5 of the specification as filed is indeed every other day for up to 4 days (*e.g.*, dosing was on day 0, day 2 and day 4 in Group A and Group B rats). Thus, the teaching of the specification as filed clearly different than the teaching of the prior art in terms of the dose to be administered, whether the animal being considered is a rat or a human. Thus, the cited references do not provide one of skill with any evidence to suggest that any dose range other than the one cited in the prior art would be useful. It is only with the specification in hand that the dose regimen as claimed is shown to be safe and effective as claimed.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations.

The claim as amended specifically recites a "1 mg/kg" dose is administered intrathecally "every other day for up to 4 days". Nowhere in the references cited by the Examiner is such a dose and dosing frequency taught or suggested. In fact, the only reference that even mentions dosage of methotrexate is limited to oral dosing amounts (see page 1244 of *Drug Facts and Comparisons* 1994). There, the dosage taught is either a single oral dose of 12 mg/week, or a divided oral dose of 2.5 mg at 12 hour intervals for 3 doses given over the course of a week (7.5 mg). Using the rat body weight, this is an oral dose of from 60 mg/kg/week for a rat (12 mg x 1/0.2 kg bw for a rat) to 12.5 mg/kg/12 hours (2.5 mg x 1/0.2 kg bw of rat). In the case of methotrexate, a highly toxic drug (see discussion in *Drug Facts and Comparisons* 1994), one of skill in the art would not be able to extrapolate an oral

dose range to an intrathecal dose range, especially going higher in dose, which would occur based on the dosing regimen claimed. Thus, a teaching of dose is lacking in the prior art cited, as well as a failure to teach use of methotrexate every other day for up to 4 days. Therefore, the combination of prior art references cited by the Examiner fails to teach or suggest each and every limitation of the claims as filed and cannot make obvious the invention of claim 1.

Moreover, a *prima facie* case of obviousness is established only when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. *In re Bell*, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). Thus, an obviousness analysis requires that the prior art both suggest the claimed subject matter and reveal a reasonable expectation of success to one reasonably skilled in the art. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). However, in the instant case, the statements made by the Examiner amount to no more than convenient assumptions about what would have been obvious to the skilled artisan at the time of the invention. However, under MPEP §2144.03, it is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record,

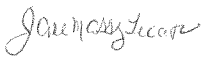
as the principal evidence upon which a rejection was based. *Zurko*, 258 F.3d at 1385, 59 USPQ2d at 1697. See also *In re Thrift*, 298 F.3d 1357, 1364, 63 USPQ2d 2002-2006 (Fed. Cir. 2002)(quoting Lee, 277 F.3d at 1344-45, 61 USPQ2d at 1435) (reliance on "common knowledge and common sense" do not fulfill the requirement to provide reasons in support of the findings of obviousness"). As a result, the Examiner's suggestion that it was *prima facie* obvious because all the claimed elements were known in the prior art is improper. Nowhere does this combination of prior art references provide one of skill with any working example of using methotrexate intrathecally for treatment of pain with radiculopathy at any dose, including the dose claimed, or at the frequency as now claimed. Accordingly, this combination of prior art references cannot establish a *prima facie* case of obviousness and withdrawal of this rejection is respectfully requested.

III. Conclusion

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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